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Development and In-vitro charaterization of transfersomes gel for the transdermal Delivery of testosterone

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Introduction

Transfersomes are recognized as agroundbreaking transdermal drug delivery system, characterized by their unique composition and enhanced permeation capabilities. These ultra-deformable vesicles consist of a lipid bilayer surrounding an inner aqueous compartment, incorporating edge activators that significantly improve their flexibility and ability to penetrate the stratum corneum. The development of ethosomes and invasomes, derived from the promising results of transfersomes, further illustrates the potential of elastic vesicle systems. Ethosomes, composed of phospholipids and high ethanol concentrations, modify the skin's lipid bilayer, while invasomes leverage terpene and ethanol to disrupt dense lipid packing for improved drug penetration. This review provides insights into the preparation, characterization, and functional mechanisms of transfersomes, highlighting their superiority over conventional liposomes. The incorporation of edge activators not only enhances deformability but also facilitates the solubilization of hydrophobic drugs, thereby optimizing drug entrapment and skin permeability. Understanding the role of various surfactants as edge activators is crucial for advancing research in elastic vesicle-based transdermal delivery systems.

Drug and excipients profile

2.2 Lecithin

2.2.1 Properties - **Density**:
- Liquid Lecithin: 0.97 g/cm³ - Powdered Lecithin: 0.5 g/cm³ - **Solubility**:
- Soluble in aliphatic and aromatic hydrocarbons, halogenated hydrocarbons, mineral oil, and fatty acids.
- Practically insoluble in cold vegetable and animal oils, polar solvents, and water.

2.2.2 Applications in Pharmaceutical Formulation or Technology

Lecithin serves multiple roles in pharmaceutical formulations:
- **Dispersing, Emulsifying, and Stabilizing Agent**: Commonly used in parenteral nutrition formulations and topical applications such as lotions and ointments.
- **Injectable Formulations**: Utilized in intramuscular and intravenous injections.
- **Intranasal Insulin Formulations**: Investigated for enhancing absorption.
- **Suppository Bases**: Reduces brittleness in suppositories.

- **Nutritional Formulations**: Integral in enteral and parenteral nutrition; phosphatidylcholine, a key component of lecithin, is essential for prenatal and newborn growth. FDA-approved infant formulas must contain choline.
- **Liposome Formulations**: Encapsulates both hydrophilic and hydrophobic drugs.

2.3 Tween 80 (Polysorbate 80)

2.3.1 Nonproprietary Names
- Polysorbate 80

2.3.2 Empirical Formula and Molecular Weight
- **Formula**: $C_{64}H_{124}O_{26}$
- **Molecular Weight**: 1310 g/mol

2.3.3 Functional Category
- Dispersing agent, emulsifying agent, nonionic surfactant, solubilizing agent, suspending agent, wetting agent.

Properties
- **Description**: Yellow oily liquid at 25°C with a characteristic odor and somewhat bitter taste.
- **HLB Value**: 15.0
- **Viscosity**: 425 mPa·s

2.3.5 Applications in Pharmaceutical Formulation or Technology - **Emulsifying Agent**:
- Used alone in oil-in-water emulsions: 1–15%
- In combination with hydrophilic emulsifiers: 1–10%
- **Water-Holding Properties**: Enhances ointment consistency: 1–10%
- **Solubilizing Agent**: For poorly soluble active ingredients in lipophilic bases: 1–15% - **Wetting Agent**: For insoluble active constituents in lipophilic bases: 0.1–3%.

2.4 Sodium Cholate

Properties
- **Molecular Formula**: $C_{24}H_{39}NaO_5$
- **Synonyms**: Cholic acid, sodium salt
- **Molecular Weight**: 430.6 g/mol
- **Solubility**: Slightly soluble in DMSO, ethanol (sonicated), methanol, and water.

Use
- Employed as a manufacturing aid for protein extraction and purification, and as a bioavailability enhancer in certain dosage forms.

2.5 Span 80 (Sorbitan Monooleate)

Properties
- **Molecular Weight**: 428.6 g/mol
- **Density**: 0.986 g/mL at 25°C

- **Vapor Pressure**: <1.4 hPa (20 °C)
- **Water Solubility**: Soluble in ethanol at 50 mg/mL; miscible with water, ethanol, isopropanol, and ether; insoluble in acetone.
- **HLB Value**: 4.3

Use

- Functions as a liquid W/O emulsifier and O/W emulsion stabilizer, particularly effective with unsaturated lipid components like oleyl alcohol or vegetable oils.
- Extensively used as a wetting agent and dispersant for materials such as zinc oxide, calamine, and penicillin in lipophilic pharmaceutical bases.

2.6 Carbopol

Properties

- **Synonyms**: Carbomera
- **Empirical Formula and Molecular Weight**: Contains 52% to 68% carboxylic acid (COOH) groups on a dry basis.

Functional Category

- Bioadhesive material, controlled-release agent, emulsifying agent, emulsion stabilizer, rheology modifier, stabilizing agent, tablet binder.

Description

Carbomers are white-colored, fluffy, acidic powders that are hygroscopic with a slight odor.

Solubility

- Swellable in water and glycerin; after neutralization, they are soluble in ethanol (95%). Carbomers do not dissolve but swell significantly due to their three-dimensional crosslinked microgel structure

Review of literature

Recent studies have focused on enhancing drug delivery systems through innovative formulations. Shamim et al. (2023) encapsulated R-carvedilol in transferosome vesicles for skin cancer chemoprevention, demonstrating improved skin penetration and retention compared to the pure drug. Their formulation, T-RCAR-3, showed no skin irritation and effectively reduced UV-induced skin inflammation and cancer development in mice. Abdallah et al. (2022) developed a Nanotransfersomal gel to enhance the hypoglycemic effects of silymarin, a compound with poor solubility and absorption. Their formulation exhibited superior transdermal flux and significantly lowered blood glucose levels compared to traditional silymarin forms. Akram et al. (2022) reviewed the role of transferosomes in transdermal drug delivery, highlighting their flexibility, biocompatibility, and ability to carry various therapeutic agents. Opatha et al. (2022) focused on a vesicular system to improve the permeation of Asiatic Acid, contributing to the ongoing research in advanced drug delivery mechanisms. Together, these studies underline the potential of transferosomal systems in enhancing drug efficacy and safety through improved delivery methods.

Rational

The primary objectives of this study are as follows:

1. **Enhancement of Testosterone Loading**: To optimize the formulation of transferosomes to achieve a higher loading capacity for testosterone, ensuring that an adequate amount of the drug is encapsulated within the vesicles for effective transdermal delivery.

2. **Improvement of Testosterone Release**: To investigate and enhance the release profile of testosterone from the transferosomal system, aiming for a controlled and sustained release that maximizes therapeutic efficacy while minimizing side effects.

3. **Study of Testosterone Presence in Transferosomes**: To analyze and confirm the existence and stability of testosterone within the transferosome formulation, utilizing various characterization techniques to ensure that the drug remains intact and bioavailable for effective transdermal absorption.

These objectives aim to leverage the unique properties of transferosomes to improve the transdermal delivery of testosterone, potentially leading to enhanced therapeutic outcomes in clinical applications.

Plan of work

This study aims to develop and characterize testosterone-loaded transferosomes for enhanced transdermal delivery. The work begins with preformulation studies, evaluating the organoleptic properties, Fourier Transform Infrared (FT-IR) Spectroscopy, UV-visible Spectroscopy, melting point, partition coefficient, and solubility of testosterone. Following this, drug-loaded transferosomes are prepared and characterized to assess their appearance, pH, drug entrapment efficiency, vesicle size, zeta potential, and morphology through electron microscopy. FT-IR analysis is performed to confirm the presence of testosterone within the transferosomes. Subsequently, a testosterone-loaded transferosome gel is formulated. The in-vitro characterization of this gel includes assessments of appearance, pH, percentage drug content, and percentage drug release. Additionally, in-vitro drug release kinetic studies are conducted to evaluate the release profile of testosterone from the gel formulation. This comprehensive approach aims to optimize the transdermal delivery system for testosterone, potentially improving its therapeutic efficacy and patient compliance.

Final experimental work

This experimental study details the materials, equipment, and methodologies employed in the characterization of testosterone for transdermal delivery. Key materials include testosterone, soy lecithin, cholesterol, and various solvents sourced from reputable suppliers. Equipment utilized comprises a bath sonicator, electronic balance, particle size analyzer, and UV spectrophotometer, among others. Preformulation studies assess the organoleptic properties, melting point, UV absorption maxima, calibration curve construction, and solubility of testosterone in different solvents. The findings from these studies are essential for optimizing the formulation and enhancing the transdermal delivery of testosterone.

Result and discussion

This section presents the results and discussions from preformulation studies of testosterone for transdermal delivery. The organoleptic properties confirmed testosterone as a white, odorless powder. Melting point analysis yielded a value of 154.33°C, consistent with literature. UV spectroscopy identified the absorption maxima at 241 nm, and a standard calibration curve demonstrated excellent linearity ($R^2 = 0.999$) within a concentration range of 1-10 µg/ml. Solubility studies indicated testosterone's highest solubility in chloroform, while it was insoluble in water. The partition coefficient was determined to be 3.436, indicating lipophilicity. FT-IR analysis showed characteristic peaks for testosterone and suggested uniform encapsulation within transferosome vesicles. These findings are crucial for optimizing testosterone formulations for effective transdermal delivery.

Summary

This study focuses on developing a testosterone-loaded transferosome gel to enhance transdermal delivery. Organoleptic evaluation confirmed testosterone as a white, odorless powder. Melting point and partition coefficient were determined at 154.33°C and 3.436, respectively. UV analysis revealed an absorption maximum at 241 nm with high linearity ($R^2 = 0.999$) within a concentration range of 1-10 µg/ml. Solubility studies indicated maximum solubility in chloroform and minimal solubility in water. The transferosome formulation TT7 achieved a drug entrapment of 83.29% with a vesicle size of 286.2 nm and a zeta potential of -26.2 mV. Incorporating TT7 into a gel with varying carbopol concentrations resulted in pH values suitable for skin application (6.167 to 6.233). In vitro drug release studies demonstrated that the transferosome gel released 95.51% of testosterone within 24 hours, following the Higuchi model ($R^2 = 0.932$). These findings support the potential of the transferosome gel for effective testosterone delivery through the skin.

Conclusion

This study demonstrates that the ethanol injection method effectively produces smallsized transferosome vesicles with improved testosterone loading and stability. The testosterone-loaded transferosome gel exhibited a significant release rate, with approximately 95.51% of testosterone being released within 24 hours, compared to only 49.58% from the control gel. These findings indicate that the transferosome gel formulation significantly enhances the transdermal permeation of testosterone, suggesting its potential for improved delivery of the drug through the skin.

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